09/937313
JC16 Rec'd PCT/PTO SEP 24 2001

TRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER 0050/49860

U.S. APPLICATION NO. (If known, see 37 CFR 1.5)

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP 00/02382	05 OCT 2000	March 17, 2000

TITLE OF INVENTION: SOLUBILIZING EXCIPIENTS IN POWDER FORM FOR SOLID PHARMACEUTICAL PRESENTATIONS

APPLICANT(S) FOR DO/EO/US Gunther BERNDL; Jörg BREITENBACH; Folker RUCHATZ; Axel SANNER and Heinrich SACK

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. /X/ This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.

2. / / This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.

3. /X/ This express request to begin national examination procedures (35 U.S.C.371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).

4. / / A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. /X/ A copy of the International Application as filed (35 U.S.C. 371(c)(2)).

   a./X/ is transmitted herewith (required only if not transmitted by the International Bureau).
   b./ / has been transmitted by the International Bureau.
   c./ / is not required, as the application was filed in the United States Receiving Office (RO/US0).

6. /X/ A translation of the International Application into English (35 U.S.C. 371(c)(2)).

7. / / Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).

   a./ / are transmitted herewith (required only if not transmitted by the International Bureau).
   b./ / have been transmitted by the International Bureau.
   c./ / have not been made; however, the time limit for making such amendments has NOT expired.
   d./ / have not been made and will not be made.

8. / / A translation of the amendments to the claims under PCT Article 19(35 U.S.C. 371(c)(3)).

9. /X/ An oath or declaration of the inventor(s)(35 U.S.C. 171(c)(4)).

10./ / A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11./ / An Information Disclosure Statement under 37 CFR 1.97 and 1.98.

12./X/ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13./X/ A FIRST preliminary amendment.
/ / A SECOND or SUBSEQUENT preliminary amendment.

14./ / A substitute specification.

15./ / A change of power of attorney and/or address letter.

16./X/ Other items or information.
International Search Report
International Preliminary Examination Report

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U.S. Appln. No. (If Known)	INTERNATIONAL APPLN. NO. PCT/EP 00/02382	ATTORNEY'S DOCKET NO. 0050/49860

17. /X/ The following fees are submitted	CALCULATIONS	PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5)): Search Report has been prepared by the EPO or JPO.....$860.00	860.00	
International preliminary examination fee paid to USPTO (37 CFR 1.482).....$690.00		
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2))).....$710.00		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO $1000.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied pro -visions of PCT Article 33(2)-(4).....$100.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 860.00	
Surcharge of $130.00 for furnishing the oath or declaration later than / / 20 / /30 months from the earliest claimed priority date (37 CFR 1.492(e)).		

Claims	Number Filed	Number Extra	Rate	
Total Claims	-20		X$18.	
Indep.Claims	-3		X$80.	
Multiple dependent claim(s)(if applicable)			+270.	
TOTAL OF ABOVE CALCULATION			=	
Reduction of ½ for filing by small entity, if applicable. Verified Small Entity statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28).				
SUBTOTAL			=	860.00
Processing fee of $130. for furnishing the English translation later than / /20 / /30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				
TOTAL NATIONAL FEE			=	860.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) $40.00 per property =				40.00
TOTAL FEES ENCLOSED			=	$ 900.00
Amount to be refunded:				$
Charged				$

a./X/ A check in the amount of $900.00 to cover the above fees is enclosed.

b./ / Please charge my Deposit Account No._____in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c./X/ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 11-0345. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b) must be filed and granted to restore the application to pending status.

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Registration No.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of)
)
BERNDL et al.) **BOX PCT**
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PCT/EP 00/02382)
Intl. Filing Date: March 17, 2000)
)
US Serial No.: TO BE ASSIGNED)
)

For: SOLUBILIZING EXCIPIENTS IN POWDER FORM FOR SOLID PHARMACEUTICAL PRESENTATIONS

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Sir:

Prior to examination of the above-identified U.S. National Stage application, kindly amend the application as follows.

CLEAN VERSION OF ALL CLAIMS

1. An excipient in powder form for use in solid pharmaceutical presentations, comprising a pharmaceutically acceptable polymer and a liquid or semisolid solubilizing surface-active substance.

2. An excipient as claimed in claim 1, comprising a surface-active substance with a drop point in the range from 20 to 40°C.

3. (amended) An excipient as claimed in claim 1, comprising a surface-active substance with an HLB of from 10 to 15.

4. (amended) An excipient as claimed in claim 1, comprising as pharmaceutically acceptable polymer a homo- or copolymer of N-vinylpyrrolidone.

5. (amended) An excipient as claimed in claim 1, comprising more than 10 and up to 70% by weight of the surface-active substance.

6. (amended) An excipient as claimed in claim 1, comprising ethoxylated sorbitan fatty acid esters as surface-active substances.

7. (amended) An excipient as claimed in claim 1, comprising products of the reaction of ethylene oxide with castor oil, hydrogenated castor oil or with 12-hydroxystearic acid as surface-active substance.

8. (amended) A process for producing excipients in powder form as claimed in claim 1, which comprises spray-drying a solution comprising the surface-active substance and the pharmaceutically acceptable polymer.

9. (amended) A process for producing excipients as claimed in claim 1, which comprises processing the constituents to a homogeneous melt in an extruder, followed by shaping.

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MARKED-UP VERSION OF AMENDED CLAIMS

3. (amended) An excipient as claimed in [either of claims 1 and 2] claim 1, comprising a surface-active substance with an HLB of from 10 to 15.

4. (amended) An excipient as claimed in [any of claims 1 to 3] claim 1, comprising as pharmaceutically acceptable polymer a homo- or copolymer of N-vinylpyrrolidone.

5. (amended) An excipient as claimed in [any of claims 1 to 4] claim 1, comprising more than 10 and up to 70% by weight of the surface-active substance.

6. (amended) An excipient as claimed in [any of claims 1 to 5] claim 1, comprising ethoxylated sorbitan fatty acid esters as surface-active substances.

7. (amended) An excipient as claimed in [any of claims 1 to 6] claim 1, comprising products of the reaction of ethylene oxide with castor oil, hydrogenated castor oil or with 12-hydroxystearic acid as surface-active substance.

8. (amended) A process for producing excipients in powder form as claimed in [any of claims 1 to 7] claim 1, which comprises spray-drying a solution comprising the surface-active substance and the pharmaceutically acceptable polymer.

9. (amended) A process for producing excipients as claimed in [any of claims 1 to 7] claim 1, which comprises processing the

constituents to a homogeneous melt in an extruder, followed by shaping.

Printed: 03-09-1999

REMARKS

The claims have been amended to eliminate multiple dependency and to place them in better form for U.S. practice. Favorable action on the application is solicited.

Respectfully submitted,

KEIL & WEINKAUF

/HBKeil

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HBK/kas

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Solubilizing excipients in powder form for solid pharmaceutical presentations

The present invention relates to excipients in powder form with high density of loading with solubilizing surface-active substances for use in solid pharmaceutical presentations, comprising a pharmaceutically acceptable polymer and a liquid or semisolid solubilizing surface-active substance.

The rate of dissolution of many active ingredients of low solubility in water can be increased by mixing with polymers such as, for example, polyvinylpyrrolidone. The mixing can take place for example by trituration, melt extrusion of polymer/active ingredient mixtures, coprecipitation, spray-drying of polymer/active ingredient solutions or granulation of active ingredient/polymer mixtures in a fluidized bed or by wet extrusion. However, the rate of dissolution and the bioavailability of such polymer/active ingredient mixtures is often inadequate.

It is generally known that the rate of dissolution and the bioavailability can be increased by adding a surface-active substance.

For example, US-A 5,834,472 discloses that it is possible to increase the bioavailability of a specific antifungal agent by use of a nonionic surface-active substance.

WO 93/11749 describes a process for producing solid dispersions of active ingredients of low solubility in water, in which firstly the active ingredient and polymeric carrier are mixed, and this mixture is then granulated with a solution of a surface-active substance in a fluidized bed. The resulting granules are then extruded using an extruder with a heating zone, followed by grinding and processing to drug forms.

However, many surface-active substances with solubilizing properties are liquid or semisolid. Solubilizers of these types are generally employed in formulations intended to be used for filling hard or soft gelatin capsules, or in solutions for intravenous or oral administration.

However, the use of such solubilizers in amounts of more than 10% by weight, based on the tablet weight, which are relevant for solubilizing active ingredients of low solubility gives rise,

because of the waxy consistency, to problems concerning the processability of the formulations.

It is an object of the present invention to find a procedure which permits larger amounts of liquid or semisolid solubilizing surface-active substances to be employed without disadvantages for the processing technique.

We have found that this object is achieved by an excipient in powder form, comprising a pharmaceutically acceptable polymer and more than 10 and up to 50% by weight, preferably 15 to 40% by weight, particularly preferably 20 to 30% by weight, based on the total amount of the excipient, of a liquid or semisolid solublizing surface-active substance.

Liquid or semisolid means for the purpose of this invention that the surface-active substance is liquid at 20°C or has a drop point in the range from 20 to 60°C, preferably 20 to 50°C, particularly preferably 20 to 40°C. The surface-active substance preferably has an HLB (hydrophilic lipophilic balance) in the range from 2 to 18, particularly preferably from 10 to 15.

A compound from the following nonionic classes is suitable as surface-active substance:

Polyoxyethylene/polyoxypropylene block copolymers (poloxamers)

Polyethylene glycols with average molecular weights in the range from 300 to 6000

Saturated and unsaturated polyglycolized glycerides like those known, for example, under the brand names Gelucire® or Labrafil® semisynthetic glycerides, fatty acid esters or ethers of fatty alcohols

Those particularly suitable are thus ethoxylated sorbitan fatty acid esters such as, for example, polyoxyethylene 20 sorbitan monolaurate, polyoxyethylene 20 sorbitan monopalmitate, polyoxyethylene 20 sorbitan monostearate, polyoxyethylene 20 sorbitan monooleate, polyoxyethylene 20 sorbitan tristearate, polyoxyethylene 20 sorbitan trioleate, polyoxyethylene 4 sorbitan monostearate, polyoxyethylene 4 sorbitan monolaurate or polyoxyethylene 4 sorbitan monooleate.

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Also suitable are sorbitan fatty acid esters such as, for example, sorbitan monolaurate.

Preferred solubilizers are products of the reaction of varying amounts of ethylene oxide with castor oil, hydrogenated castor oil or 12-hydroxystearic acid,
for example polyoxyethylene glycerol ricinoleate 35, polyoxyethylene glycerol trihydroxystearate or PEG 660-12-hydroxystearate (polyglycol ester of 12-hydroxystearic acid with 30 mol% of ethylene glycol).

Macrogol 6 cetylstearyl ether or macrogol 25 cetylstearyl ether are likewise suitable.

Particularly suitable pharmaceutically acceptable polymeric carrier materials for the excipient according to the invention are water-soluble polymers. Preference is given to homo- or copolymers of N-vinylpyrrolidone with Fikentscher K values of from 12 to 100, preferably 17 to 30, for example polyvinylpyrrolidone, copolymers with vinyl acetate or vinyl propionate such as, for example, copovidone (VP/VAc-60/40).

Also suitable are polyvinyl alcohol, and polyvinyl acetate which may also be partly hydrolyzed. Acrylate polymers of the Eudragit type are likewise suitable.

Suitable polymers are also cellulose derivatives such as alkylcelluloses, hydroxyalkylcelluloses or hydroxyalkylcelluloses, for example ethylcellulose or hydroxypropylcellulose.

The excipients can be produced in various ways. Thus, for example, the solubilizer can be added to a solution of the polymer, and the solvent can then be removed. Suitable solvents are, in particular, water, but also ethanol or longer-chain alcohols such as isopropanol, propanol, butanols or else acetone or mixtures of such solvents. Spray-drying is the preferred drying process.

The excipients can also be produced by granulation processes known per se, such as, for example, fluidized bed granulation, in which case a liquid phase containing the solubilizer is sprayed onto the solid carrier.

The excipients in powder form can also be produced by melt extrusion in the absence of solvents. During the melt extrusion, the liquid solubilizer phase can be metered into the extruder

continuously or batchwise. The melt thus obtained can be processed to powders in various ways.

Thus, the extrudate emerging through a die or breaker plate can be granulated by conventional techniques, in particular the hot-cup technique, and, where appropriate, also ground. The melt can also be extruded through the open extruder head, likewise resulting in pellets. The solubilizer-containing excipient can also be compressed to tablets by calendering and then be ground. The grinding may additionally take place in the extruder, or granulation can take place in so-called roll mills.

If desired, the solubilizer-containing powders according to the invention may also comprise other excipients, for example flow regulators, dyes, mold release agents, fats and waxes, disintegrants, bulking agents and other conventional tableting excipients such as, for example, sugars, sugar alcohols or starch degradation products.

The powders according to the invention are free-flowing and preferably have particle sizes of from 10 to 1000 μ.

They can be processed without restriction for producing solid forms which can be administered orally, such as tablets, microtablets, sachet fillings, effervescent tablets, suckable tablets, pellets or pastilles. Such forms can be produced by conventional pharmaceutical processes such as melt extrusion, tableting by compression or paste extrusion with subsequent shaping.

The powders according to the invention are suitable in principle for formulations of all pharmaceutical, cosmetic or dietary active ingredients. It is particularly suitable for formulations of CNS-active substances, dihydropyridine derivatives, protease inhibitors, reverse transcriptase inhibitors, antimycotics or cytostatics.

A particular advantage of the powders according to the invention is also that other liquid substances such as, for example, oils can be incorporated into the excipient in powder form and then lead, especially in the case of oil-soluble active ingredients, to an improvement in the bioavailability.

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Examples

Example 1

1.65 l of a 20% strength aqueous solution (m/V) of Cremophor RH 40 (product of the reaction of 1 mol of hydrogenated castor oil with 45 mol of ethylene oxide) were stirred at room temperature into 5 l of a 20% strength aqueous solution (m/V) of polyvinylpyrrolidone with a K value of 30 (Kollidon 30). The solution resulting from this was then spray-dried to result in a fine powder.

Example 2

2 kg/h of a copolymer of 60% by weight of vinylpyrrolidone and 40% by weight of vinyl acetate with a K value of 30 were metered by means of a weigher into a twin screw extruder (ZSK 30 Werner & Pfleiderer). At the same time, molten Cremophor RH 40 was continuously metered into section 3 of the extruder by pump at a rate of 0.5 kg/h. The mixture was homogenized and plastified in the extruder and then calendered.
Temperatures [°C]: 30 78 120 109 110 110
Die [°C]: 103
Vacuum: 80 mbar
The calendered moldings were ground using a ring sieve mill from Retsch (2 mm sieve).

Tableting

50% by weight of the resulting powder were compressed with 10% by weight of crospovidone, 10% by weight of Ca silicate, 8.5% by weight of microcrystalline cellulose, 20% by weight of cyclosporin, 0.5% by weight of Mg stearate and 1% by weight of Aerosil (highly dispersed silica) to give 500 mg tablets.

Example 3

A copolymer of 60% by weight of vinylpyrrolidone and 40% by weight of vinyl acetate with a K value of 30 was metered at 2 kg/h by means of a weigher into a twin screw extruder (ZSK 30 Werner & Pfleiderer). At the same time, molten Cremophor RH 40 mixed with 20% by weight of corn oil was metered continuously into section 3 of the extruder by pump at a rate of 0.5 kg/h. The mixture was homogenized and plastified in the extruder and then calendered. The finished mixture contained:

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80% by weight of Kollidon VA 64 (copovidon)
16% by weight of Cremophor RH 40
4% by weight of corn oil
Temperatures [°C]: 30 70 115 105 105 105
Die [°C]: 103
Vacuum: 80 mbar

Printed: 03.04.2003

We claim:

1. An excipient in powder form for use in solid pharmaceutical presentations, comprising a pharmaceutically acceptable polymer and a liquid or semisolid solubilizing surface-active substance.

2. An excipient as claimed in claim 1, comprising a surface-active substance with a drop point in the range from 20 to 40°C.

3. An excipient as claimed in either of claims 1 and 2, comprising a surface-active substance with an HLB of from 10 to 15.

4. An excipient as claimed in any of claims 1 to 3, comprising as pharmaceutically acceptable polymer a homo- or copolymer of N-vinylpyrrolidone.

5. An excipient as claimed in any of claims 1 to 4, comprising more than 10 and up to 70% by weight of the surface-active substance.

6. An excipient as claimed in any of claims 1 to 5, comprising ethoxylated sorbitan fatty acid esters as surface-active substances.

7. An excipient as claimed in any of claims 1 to 6, comprising products of the reaction of ethylene oxide with castor oil, hydrogenated castor oil or with 12-hydroxystearic acid as surface-active substance.

8. A process for producing excipients in powder form as claimed in any of claims 1 to 7, which comprises spray-drying a solution comprising the surface-active substance and the pharmaceutically acceptable polymer.

9. A process for producing excipients as claimed in any of claims 1 to 7, which comprises processing the constituents to a homogeneous melt in an extruder, followed by shaping.

Solubilizing excipients in powder form for solid pharmaceutical presentations

Abstract

The invention relates to excipients in powder form for use in solid pharmaceutical presentations, comprising a pharmaceutically acceptable polymer and a liquid or semisolid solubilizing surface-active substance.

Declaration, Power of Attorney

0050/049860

We (I), the undersigned inventor(s), hereby declare(s) that:

My residence, post office address and citizenship are as stated below next to my name,

We (I) believe that we are (I am) the original, first, and joint (sole) inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled

Solubilizing excipients in powder form for solid pharmaceutical presentations

the specification of which

[x] is attached hereto.

[ ] was filed on _____ as

Application Serial No. _____

and amended on _____.

[x] was filed as PCT international application

Number PCT/EP00/02382

on 17/03/2000

and was amended under PCT Article 19

on _____ (if applicable).

We (I) hereby state that we (I) have reviewed and understand the contents of the above–identified specification, including the claims, as amended by any amendment referred to above.

We (I) acknowledge the duty to disclose information known to be material to the patentability of this application as defined in Section 1.56 of Title 37 Code of Federal Regulations.

We (I) hereby claim foreign priority benefits under 35 U.S.C. § 119(a)–(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed. Prior Foreign Application(s)

Application No.	**Country**	**Day/Month/Year**	**Priority Claimed**	
19913606.8	*Germany*	*25 March 1999*	[x] Yes	[ ] No

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We (I) hereby claim the benefit under Title 35, United States Codes, § 119(e) of any United States provisional application(s) listed below.

(Application Number)	(Filing Date)
(Application Number)	(Filing Date)

We (I) hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

Application Serial No.	**Filing Date**	**Status (pending, patented, abandoned)**

And we (I) hereby appoint **Messrs. HERBERT. B. KEIL**, Registration Number 18,967; and **RUSSEL E. WEINKAUF**, Registration Number 18, 495; the address of both being Messrs. Keil & Weinkauf, 1101 Connecticut Ave., N.W., Washington, D.C. 20036 (telephone 202–659–0100), our attorneys, with full power of substitution and revocation, to prosecute this application, to make alterations and amendments therein, to sign the drawings, to receive the patent, and to transact all business in the Patent Office connected therewith.

We (I) declare that all statements made herein of our (my) own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Docket No. 0050/049860

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1-10

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